REMARKS

STATUS OF THE CLAIMS

Claims 118-183 were pending in the application and remain rejected under 35 U.S.C. § 112, first paragraph (enablement). New claims 184 and 185 are newly presently as shown above. Support for these claims is found, for example, at page 44, lines 7-13 and lines 20-21. Thus, claims 118-185 are presently pending as shown above.

INTERVIEW SUMMARY

A personal interview with Examiner Brusca was conducted on February 19, 2004 by co-inventor Dr. Casey Case and Sean Brennan. At the interview, the following items were discussed:

1. It was agreed that methods for protein delivery, other than liposomes, are disclosed in the specification, for example, at page 43, line 31 through page 47, line 7.

2. The Examiner suggested that the description of Figure 5 of Dr. Case' declaration, mailed on October 30, 2003 (hereinafter "the first Case Declaration") explicitly recite that protein was delivered to the cells.

3. The Examiner suggested that Applicants provide additional data, similar to that disclosed in Figure 6 of the first Case Declaration, showing modulation of gene expression following delivery, to an animal, of a protein comprising an *Antennapedia* domain.

Applicants thank Examiner Brusca for his time and effort in discussing these issues, and for his suggestions for overcoming the outstanding rejection.

35 U.S.C. § 112, FIRST PARAGRAPH

The rejection of claims 118-183 as allegedly not enabled for methods in which a ZFP polypeptide is delivered to a cell has been maintained. (Advisory Action, page 2). The arguments, declaration and additional evidence filed were deemed unpersuasive. In addition, during the interview the Examiner requested that Figure 5 of the first Case Declaration be more fully explained and, furthermore, that additional data be provided, showing modulation of gene expression following *in vivo* delivery of a protein using an *Antennapedia* peptide.

With regard to Figure 5 of the first Case Declaration, Applicants point out that the first sentence of paragraph 5 of the first Case Declaration clearly indicated that Figure 5 depicted results obtained following protein administration:

> 5. Figures 3-6 of Exhibit B show that VEGF expression was enhanced *in vivo* and *in vitro* upon a single application of ZFP-IS fusion proteins. ... Figure 5 demonstrates that both EP and AP internalization sequences significantly increase the levels of VEGF mRNA in cells. (paragraph 5 of first Case Declaration).

Nonetheless, to further clarify, another Declaration by Dr. Case (hereinafter "the second Case Declaration") is attached hereto. Dr. Case specifically states that the data shown in Figure 5 was obtained following delivery of VEGF-targeted ZFPs in protein form. *See,* paragraphs 4 and 5 of the second Case Declaration).

Furthermore, as requested by the Examiner Dr. Case's second Declaration also submits data establishing that zinc finger proteins modulate gene expression *in vivo* when administered as proteins using an *Antennapedia* peptide as described in the specification:

> 6. Data, attached hereto, show that ZFPs prepared and delivered as peptides according to the teachings of the specification can be utilized *in vivo* to modulate gene expression and facilitate angiogenesis. In particular, an established model system for determining angiogenesis is evaluation of vessel formation in the murine ear. Using this system, the number of blood vessels observed after injection of a mouse ear with ZFP-*Antennapedia* fusion proteins was evaluated. Exhibit A, entitled "Experimental Protocols," provides details on these and other protocols used in our studies. As set forth in Exhibit A, administration of VEGF-targeted ZFPs to live animals was conducted essentially as described on page 49, lines 10-13 and 27.
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> 7. Exhibit B attached hereto contains photographs showing increased vascularity in mouse ear following injection of a ZFP in the ear. The left photograph shows an ear that had been injected with a protein comprising a VEGF-targeted ZFP (VOP32E), a transcriptional activation domain and the *Antennapedia* translocation domain. The right photograph shows an ear that had been injected with an internalization peptide only. comparison of the two photographs indicates that the ZFP-injected ear show[s] a higher degree of vascularity. Thus, using the accepted live mouse model system for angiogenesis, it has been demonstrated that VEGF-targeted ZFPs delivered as proteins using an *Antennapedia* translocation domain as described in the specification, modulate vessel formation.
>
> 8. In addition, protein-mediated delivery of VEGF-targeted ZFPs enhanced VEGF expression in muscle *in vivo*. Exhibit C shows increased VEGF expression in mouse skeletal muscle obtained from a mouse injected in a hindlimb

> muscle with a solution containing a fusion protein comprising a VEGF-targeted ZFP, a transcriptional activation domain and the *Antennapedia* translocation domain. Internal standards indicated that enhancement of VEGF expression in these tissues is not due to injection of protein *per se*. These studies demonstrate that ZFPs, administered as fusion proteins comprising an *Antennapedia* translocation domain according to the teachings of the specification, regulate gene expression *in vivo*.

This evidence further demonstrates that fusion proteins comprising engineered ZFPs and membrane translocation peptides such as those derived from *Antennapedia* (see, *e.g.*, page 44 of the specification) can be used to modulate expression of endogenous genes in living animals when delivered as proteins.

Thus, Applicants have provided ample factual evidence demonstrating that the specification enables the pending claims throughout their scope, and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants believe that the claimed subject matter is fully enabled in light of the teachings of the specification, and evidence of record (including data supplied herein and previously). If any issues remain to be addressed, the Examiner is encouraged to telephone the undersigned at (650) 493-3400.

Respectfully submitted,

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